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Anti-Ulcerogenic Evaluation of *Torilis Leptophylla* Plant Extract on Indomethacin Induced Mice Gastric Ulcer

[1]Saba Batool, [2]Sheikh Maria Qammar,[3]Tooba Malik, [4]Naseem Saud Ahmad, [5]Bushra Shaheen,[6] Javaria Fatima

[1]*Department of Pharmacology, Nishtar Medical University, Multan*
[2]*Department of Pharmacology, Rashid Latif Medical and Dental College, Lahore*
[3] *Department of Pharmacology, Services Institute of Medical Sciences, Lahore*
[4]*Department of Pharmacology, Superior University, Lahore*
[5]*Department of Pharmacology, Bakhtawar Amin Medical and Dental College, Multan*
[6]*Department of Pharmacology, Fatima Jinnah Medical University, Lahore*

ABSTRACT

Introduction: Despite conventional anti-ulcer therapies for peptic ulcer diseases, medicinal plants might provide effective new anti-ulcer compounds or, alternatively, as adjuncts to existing therapies.
Aims & Objectives: To evaluate the effects of *Torilis leptophylla* on indomethacin-induced gastric ulcer in mice.
Place and duration of study: It was an experimental study carried out in the Department of Pharmacology, University of Health Sciences, Lahore, from March to December 2016.
Material & Methods: Thirty six (36) adult healthy male BALB/C mice were divided equally in 6 groups and assigned as group I (control), group II (positive control), group III–V (TLM low, medium and high dose) and group VI (omeprazole). Gastric ulcers were induced by oral ingestion of indomethacin in groups II -VI. Acute oral toxicity of the plant was also tested. Antiulcer effect was assessed by measuring body weight, amount and pH of gastric juice, ulcer count, severity of gastric lesion, ulcer index, percentage (%) inhibition of ulcer and histopathology of gastric tissue. Results were analyzed by SPSS 20.0, P-value<0.05 was considered significant.
Results: Gastric ulcer reduced the body weight in indomethacin induced animals (28 ± 2.53, 29.66 ± 3.88, 29.66 ± 2.33, 31 ± 3.52,32 ± 3.099 g in group II, III, IV, V and VI respectively) at day 3. Omeprazole and TLM treated groups reduced the gastric volume and pH as compared to positive control. Ulcer index (18.83, 5.14, 3.42, 1.71, 1.76 of the group II, III, IV, V and VI respectively) depicted significant reduction by treatment groups. Ulcer's percentage inhibition (72.7, 81.8, 90.88, 90.65 of low, median and high dose of TLM and standard drug respectively) was increased. Histopathological observations were remarkably reversed by TLM treated groups.
Conclusion: *Torilis leptophylla* could significantly protect gastric mucosa from damage by indomethacin.

Keywords: Gastric ulcer, indomethacin, omeprazole, *Torilis leptophylla.*

INTRODUCTION

Peptic ulcer disease (PUD) is one of the major gastro-intestinal ailments, affecting 5-15% of the global population[1]. PUD has been a crucial problem of morbidity and mortality throughout the world. Perforated ulcer is a life-threatening condition and prevalence of gastrointestinal hemorrhage is associated with mortality approaching 10 - 40 % and high recurrence[2].
Ulcers are usually triggered by an imbalance between various defensive and aggressive factors within the alimentary canal. There are many protective factors like bicarbonates, mucus, mucosal blood flow, prostaglandins (PGs), glutathione and nitric oxide. Gastroduodenal ulcersare aggravated by increase gastric acid and pepsin production, *Helicobacter pylori* colonization, use of non-steroidal anti-inflammatory drugs (NSAIDs), alcoholic beverages, oxidative stress and ischemia followed by reperfusion[3]. NSAIDs are among the most widely used analgesics, antipyretics and anti-inflammatory drugs in the world and are considered to substantially increase the risk of various gastrointestinal ailments[4].
Conventionally, drugs like antacids, anti-cholinergics, proton pump inhibitors (PPIs), H2 receptor blockers and cytoprotective agents are used as antiulcer drugs. Some drugs are not highly efficient due to their drug interactions with cytochrome enzymes and unpleasant side effects like gastric acid suppression, diarrhea, delayed food absorption, hypomagnesemia, low vitamin B_{12} and antiandrogen effects etc[5]. However,

alternative herbal and complementary medicines have attained global popularity due to their widespread use in the field of medicine for treating many diseases[6].

An annual herb, *Torilis leptophylla,* found in hilly areas of Margalla, Hazara and Kashmir[5]. *T. leptophylla* has been used traditionally for prevention and cure of gastrointestinal ailments in Pakistan[6]. Preliminary phytochemical screening of *T. leptophylla* methanolic extract (TLM) proved the presence of flavonoids, alkaloids, phlobatannins, tannins and terpenoids [7].

Recent study has reported its protective effect in CCl4 induced hepatotoxicity owing to its antioxidant properties[8]. Fruit extract of *T. leptophylla* showed significant inhibition of growth of numerous gram positive and gram-negative pathogens[9]. Limited studies have been carried out to determine the effect of *T.leptophylla* on gastric ulcer according to available data. In the light of composition and therapeutic protection in folk medicine, this research work was designed to assess the effect of TLM on indomethacin induced gastric ulcer in mice.

MATERIAL AND METHODS

This experimental study has been performed under standard guidelines issued by Ethical Review Committee for Medical and Biomedical Research, UHS, Lahoreduring the year 2016. The fresh flowering shoots of *T. leptophylla* were collected in April, 2016 from the Botanical Garden, Quaid-e- Azam University, Islamabad. The plant specimen was submitted to Director, National Agriculture Research Centre (NARC), Islamabad for identification and authentication. Dried shoots of *T. leptophylla* were crushed and soaked in 95% methanol at 25°C for 72-hrs. The resultant mixture was filtered and concentrated by rotary evaporator under low pressure at 40°C. The concentrate was freeze dried by lyophilizer and stored at -4 °C for further pharmacological evaluation[10]. Thirty-six adultmale healthy BALB/c mice (25-35 g) were randomly grouped into six (n=6). All animals were acclimatized for one week before the start of study. They were kept at controlled room temperature (22-24°C), humidity (45-65%) and natural 12/12h light and dark cycle. Mice were fed on rodent chow and free access to water *ad libitum*. Indomethacin and Omeprazole were procured from local pharmacy. Gum acacia, formalin, methanol, ethanol, dimethyl sulfoxide (DMSO), xylene, eosin stain, hematoxylin stain and paraffin wax of pharmaceutical grade were purchased from local supplier.

Acute Oral Toxicity

Twelve mice were randomly allotted into three groups (n=4) and kept at overnight fasting before experiment with free excess to water. TLM extract in dose of 1 g/kg b.w, 2 g/kg b.w and 3 g/kg b.w by gavage to group A, group B and group C respectively as single dose. TLM extract in dose of 1 g/kg b.w, to group A The mice were observed closely for the first 4h and then after every 6 h for next 48 h of TLM administration to observe any change in behavior, food intake, urination, stool consistency, rate of respiration or symptoms of toxicity and even mortality [11].

Experimental setup:

Induction of Gastric Ulcer:

Gastric ulcer was induced by oral administration of indomethacin (20 mg/ kg, single dose)[12,13]. Mice were kept deprived of food but had free access to water, 24-hrs prior to drug administration. Antiulcer therapy was commenced 6 hours after induction of ulcer in groups III- VI and administered once daily for 3 days through gavage as per group designation.

Experimental Groups:

Group I (control):

Ulcer induced animals were given distilled water as vehicle by gavage daily for 3 days.

Group II (positive control): Vehicle used as solvent for test compound

Group III (low dose):

Ulcer induced animals were given TLM 100 mg /kg b.w.

Group IV (median dose):

Ulcer induced animals were given TLM 200 mg /kg b.w.

Group V (high dose):

Ulcer induced animals were given TLM 300 mg /kg b.w.

Group VI (Standard):

Ulcer induced animals were given omeprazole 3 mg/kg b.w[14].

Evaluation of Body Weight:

Body weight of mice were evaluated by using digital weighing balance at day zero before induction of gastric ulcer and 3 hours after the last dose of test compounds on 3rd day. Variation in body weight was observed[15].

Euthanization:

All experimental mice were anesthetized on3rd day,4 hours after the last dose and sacrificed.

Determination of Gastric Juice Volume and pH:

The effects of *T. leptophylla* on volume of gastric juice (µl) and pH were determined[16].

Macroscopic Examination of Stomach:

The stomach of each was excised along the greater curvature. The mucosal surface of each stomach was examined for gross lesions. The number of ulcers was counted per animal. Scoring of ulcers was made as follows i.e, 0 = No ulcer; 0.5 = congested mucosa; 1 = Superficial ulcer; 2 = Deep ulcer; 3 = Perforation[17]. The ulcer index (UI) was measured[17]

UI = $(UN + US + UP) \times 10^{-1}$

Where;

UN = Average number of ulcers per animal.

US = Average number of severity scores.

UP = Percentage of animals with ulcer.

Percentage inhibition of ulceration was determined by equation[17].

$$\% \text{ Inhibition of ulceration} = \frac{(\text{UI control} - \text{UI test}) \times 100}{\text{UI control}}$$

Microscopic Examination of Stomach:

Gastric tissues were fixed in 10% formaldehyde solution then dehydrated with alcohol, cleared in xylene and embedded in a paraffin wax. Slides were stained with hematoxylin and eosin[16]. Histopathological scoring was done according to the criteria used by Syed and his colleagues[3].

Statistical data analysis:

The results were analyzed by SPSS 20.0. Quantitative data was described in the form of mean ±S.D. Normality of data distribution within each group is determined by using the Shapiro-Wilk Test. One way ANOVA was applied followed by post hoc Tukey's test. A *P*-value ≤ 0.05 was considered as statistically significant.

RESULTS

Oral Acute Toxicity:

Observations	Group A TLM (1 g/kg b.w)	Group B TLM (2 g/kg b.w)	Group B TLM (3 g/kg b.w)
Body weight	Normal	Normal	Normal
Dietary Habits	Normal	Normal	Normal
Stool consistency	No significant change	No significant change	No significant change
Urination	No significant change	No significant change	No significant change
Behavior	No significant change	No significant change	No significant change
Rate of respiration	No change in rate	No change in rate	No change in rate
Drowsiness	Absent	Absent	Absent
Alertness	Active	Active	Active
Mortality	Nil	Nil	Nil

Table-1: General Appearance and Behavioral Observations in oral Acute Toxicity of TLM in Mice (n=4).

In the study of acute toxicity, no visible signs of toxicity were noted as shown in Table-1.

Effect of TLM on Body Weight in Mice:

At day 3, body weight was highest in control (group I) and lowest in positive control (group II) (p value ≤ 0.05). Body weight was higher in TLM high dose treated (group V) and omeprazole treated (group VI) in comparison of group II with p value ≤ 0.05. It was insignificantly higher in groups III and VI than group II (Table-2).

Group	Treatment	Weight (g)		
		Body Weight (g) at Day (0)	Body Weight (g) at Day (3)	Weight difference (g)
I	**Control**	29.33± 3.011	32.33± 3.44	3 ± 0.429
II	**Positive control**	29.66± 2.65	28± 2.53	-1.66± 0.13*
III	**TLM (Low dose)**	30.33± 2.33	29.66± 3.88	-0.67± 1.55
IV	**TLM (median dose)**	28.66± 2.065	29.66± 2.33	1± 0.27
V	**TLM (high dose)**	29± 3.28	31± 3.52	2± 0.24**
VI	**Omeprazol (Standard drug)**	29.66± 2.94	32± 3.099	2.34 ± 0.159**

Table-2: Effect of TLM on Body Weight in Indomethacin Induced Gastric Ulcer in Mice (n=6).

Independent- Samples T-Test was applied and results are presented as Mean ± S.D.

P-value< 0.05 is expressed by*and**,where* shows a significant difference of group II with group I and,**shows a significant difference of group II with group V and VI.

Effect of TLM on Volume of Gastric Juice and pH:

Stomach juice volume of group II was significantly (p≤0.05) higher in comparison of group I. TLM treated groups showed significant reduction of secretion volume (p ≤ 0.05) than group II. Group VI represented significant decrease (p ≤ 0.05) in volume of gastric juice than positive control. A reduction in gastric juice volume in group VI and among TLM treatment groups III to V was almost same (Table-3). Similarly, significant decrease in pH (p ≤ 0.05) was observed in group II than group I. Gastric pH was significantly increased (p ≤ 0.05) in TLM treated group III. A significant rise (p ≤ 0.05) in gastric pH was observed in group VI. An increment in gastric pH of group IV- VI was the same (Table-3).

Results are tabulated as Mean ± S.D.P- value< 0.05 is expressed by*and**where*shows a significant difference between group I (control)

and group II (positive control), and ** shows significant difference of treatment groups than group II.

Effect of TLM on Gastric Lesions:

Treatment with TLM (100, 200 and 300 mg/kg) and omeprazole (3 mg/kg) determined the significant reduction of the ulcer index, number of lesions, and ulcer percentage than the control group ($p < 0.05$) (Table-4).

Results are presented as Mean ± SEM. P-value<0.05 is denoted by * and** where *and shows a significant difference of group II with group I and **shows a significant difference of treatment groups with group II.

Group	Treatment	Gastric volume (µl)	pH
I	Control	400 ± 77.04	5.52 ± 0.741
II	Positive control	790 ± 80.10*	3.47 ± 0.581*
III	TLM (Low dose)	620 ± 75.83**	4.73 ± 0.633**
IV	TLM (Median dose)	600 ± 89.33**	5.06 ± 0.688**
V	TLM (High dose)	570 ± 44.72**	5.1 ± 0.362**
VI	Omeprazole (Standard drug)	540 ± 66.45**	4.91 ± 0.350**

Table-3: Effect of TLM on Volume of Gastric Juice (µl) and pH in Indomethacin Induced Gastric Ulcer in Mice (n=6).

Group	Treatment	Average number of ulcers per animal (UN)	Average number of ulcer severity score (US)	Ulcer index (UI)	% Inhibi-tion
I	Control	0	0	0	-
II	Positive control	1.83± 0.02*	3.16± 0.014*	18.83	-
III	TLM (Low dose)	0.5± 0.015**	0.91± 0.018**	5.14	72.70
IV	TLM (Median dose)	0.33± 0.014**	0.75± 0.017**	3.42	81.80
V	TLM (High dose)	0.16± 0.011**	0.41± 0.016**	1.71	90.88
VI	Omeprazole (Standard drug)	0.33± 0.01**	0.83± 0.014**	1.76	90.65

Table-4: Effect of TLM on Gastric Lesions in Indomethacin Induced Gastric Ulcer in Mice (n=6).

Histopathological Assessment of Gastric Tissues:

All the parameters of microscopic observations of gastric tissue in control (group I) demonstrated normal architecture. Mucosa was intact from innermost mucosal layer to outermost serosal layer. No inflammatory cell infiltration, hemorrhage or edema was observed in the submucosal regions (Fig-1). Positive control (Group II) showed signs of severe injury that included ulcers, erosions, hemorrhage, inflammation and vasocongestion in all gastric tissues (Fig-2). TLM treated groups (group III-V) and omeprazole treated (group VI) showed significant improvement of gastric tissue integrity and histopathological changes (Table-5; Fig-3 & Fig-6).

Each observation was scored as: Present = 1 and absent = 0. A cumulative score was expressed in percentages (%). Fishers Exact Test was applied. P value < 0.05 is expressed by*where*shows a significant difference of group IV- VI with group II (positive control).

Observ-ation (%)	Group I Control	Group II Posi-tive Control	Group III TLM 100 mg/ kg	Group IV TLM 200 mg/kg	Group V TLM 300 mg/kg	Group VI ome-prazole
Erosion	0	6 (100)	3 (50)	2 (33.3)	2 (33.3)	2 (33.3)
Hemorrha ge	0	6 (100)	2 (33.3)	1 (16.6)*	1 (16.6)*	1 (16.6)*
Ulcer	0	6 (100)	2 (33.3)	1 (16.6)*	1 (16.6)*	1 (16.6)*
Inflammati on	0	6 (100)	4 (66.6)	3 (50)	2 (33.3)	4 (66.6)
Edema	0	3 (50)	2 (33.3)	1 (16.6)	0	1 (16.6)
Fibrinoid-necrosis	0	2 (33.3)	1 (16.6)	0	0	0
Vaso-congestion	0	6 (100)	2 (33.3)	2 (33.3)	1 (16.6)*	1 (16.6)*
Fibrosis	0	2 (33.3)	0	0	0	1 (16.6)

Table-5: Effect of TLM on Histological Parameters in Indomethacin Induced Gastric Ulcer in Mice (n=6).

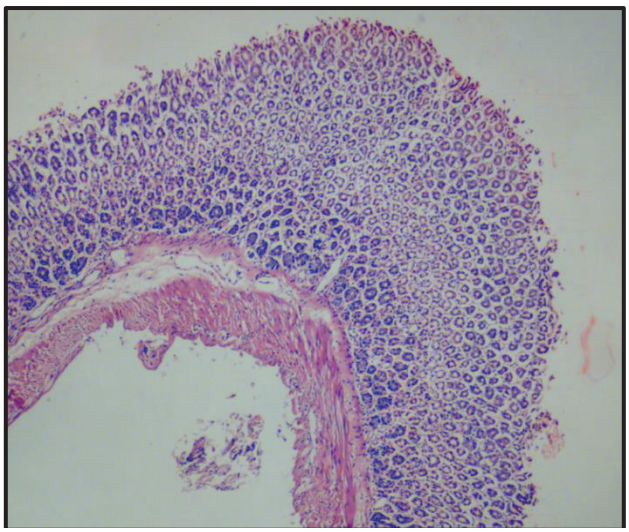

Fig-1: Photomicrograph of Group I –(control). Intact mucosa, submucosa and muscularis layer.

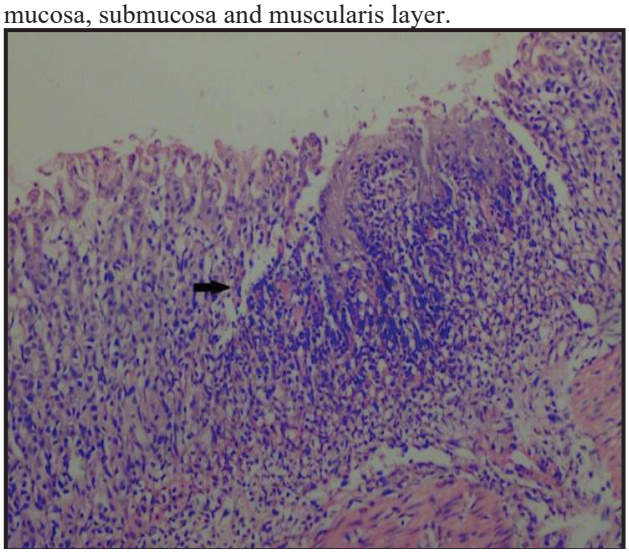

Fig-2: Photomicrograph of Group II (positive control) disruption, erosions of mucosal layers and numerous inflammatory cells.

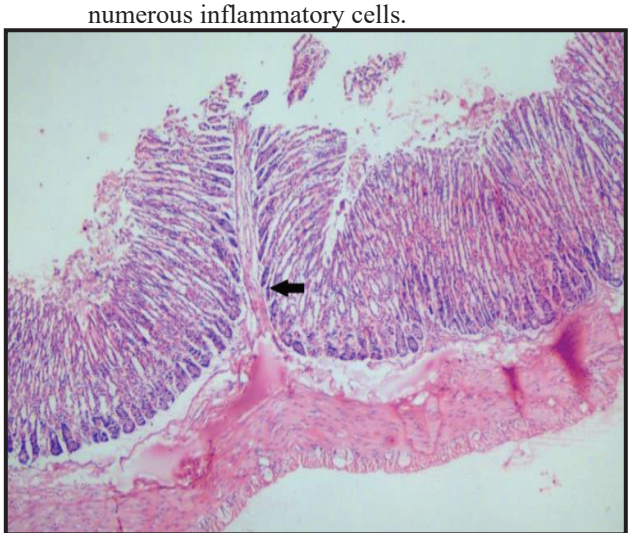

Fig-3: Photomicrograph of Group III (TLM 100mg/kg). Inflammatory cells and fibrosis.

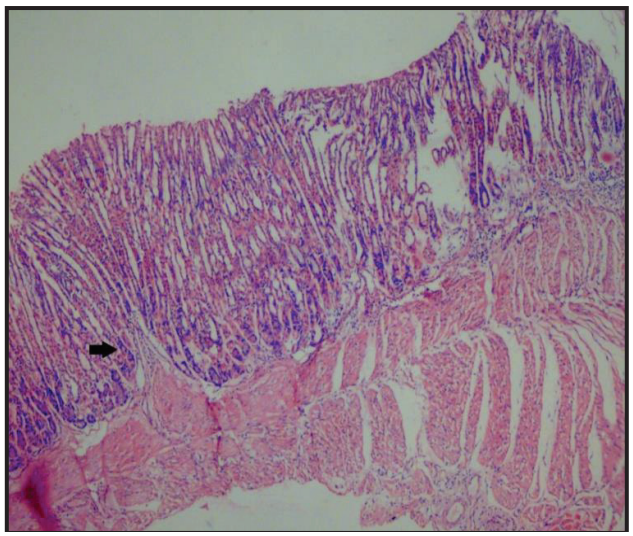

Fig-4: Photomicrograph of Group IV (TLM 200mg/kg); intact mucosa with mild focal disruption and few inflammatory cells

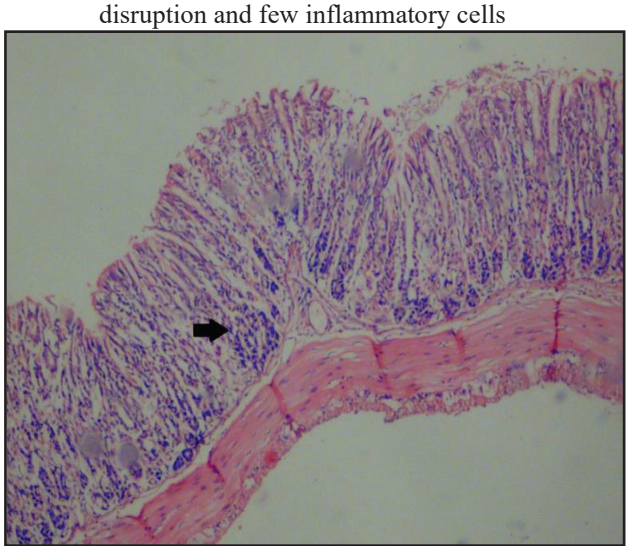

Fig-5: Photomicrograph of Group V (TLM 300mg/kg) Normal intact mucosa with mild focal disruptions and inflammatory cells.

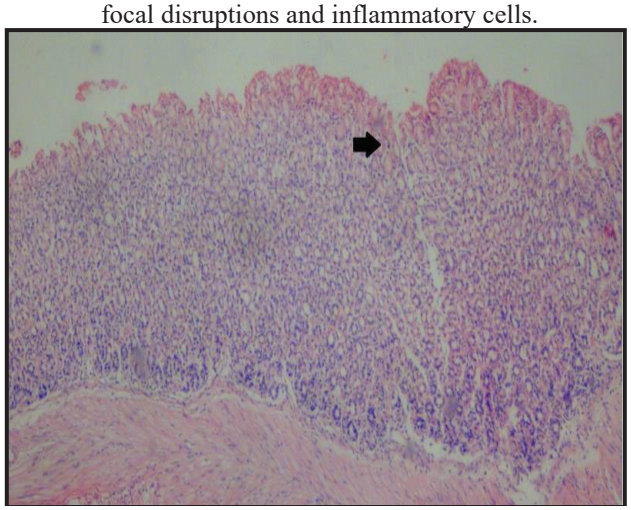

Fig-6: Photomicrograph of Group VI (omeprazole 3mg/kg) intact mucosa with mild erosions and few inflammatory cells.

DISCUSSION

Acute oral toxicity of TLM did not demonstrate any change in behavior, food intake, body weight, stool consistency, urination, mental alertness, or other signs of toxicity even mortality of experimental animals. These findings encouraged us to use TLM for this study by gavage in appropriate doses.

Ramaswamy et al. (2010) presented 46 % decrease in gastric juice volume by standard drug (omeprazole) and 50 % decrease by *Trachys permumammi* extract[18]. Sofidiya et al. (2012) reported a 10 % decrease in gastric juice volume by standard drug (cimetidine) and 77 % decrease by *Flabella riapaniculata* extract treated group. Better results of Sofidiya et al. (2012) may be due to better anti-secretory effects of the plant[19].

In current work, gastric pH was 37% decreased in diseased group as compared to healthy group.TLM treatment groups showed increase in gastric pH by 27 %with minimum dose, 32 % with median as well as maximum doses in comparison with diseased group. Increased gastric pH by 30% was also observed in group VI than diseased group. Gastric pH was 3.7 % lowered in group III whereas 3% and 4% raised in group IV and group V respectively than group VI. Ramaswamy et al. (2010) have reported analogous results to the present study with 21.5 % increase in gastric pH by omeprazole and 27% increase by the *Trachys permumammi*extract[18].

Ulcerated group showed apparent lesions in superficial as well as in deep layers of stomach. There was marked congestion, loss of normal rugae and mucosal hemorrhagic areas at or near the ulcer sites. Average number of ulcers (UN) declined by 73% with minimum, 82 % with median and 91.3 % with maximum dose of TLM as compared to diseased group. Correspondingly, omeprazole has also decreased the ulcer count by 82 % than group II. Higher count of ulcer by 34 % was observed in group III than standard drug. Maximum dose of plant extract demonstrated 50 % decrease in UN as compared to omeprazole. Overall effect showed a decline in average number of ulcers by both plant extract and omeprazole treatment groups.

Ulcer score (US) was also suppressed significantly in plant treated groups by 72%, 77% and 87% in groups III, IV and V respectively than group II. Standard drug also depicted a significant decrease in US by 74% as compared to positive control group. Omeprazole demonstrated 9 % decline in US as compared to group III. A decrease in ulcer score observed by 10 % and 50 % in groups IV and V respectively as compared to group VI. Severity of lesions induced by Indomethacin was diminished by plant extract and omeprazole as well.

Ulcer index (UI) clearly explained that TLM possess anti-ulcerogenic activity in dose dependent manner. Plant extract has lowered UI by 90 %, 82 % and 72 % with low, median and high doses respectively as compared to diseased group. Standard group showed reduction in UI by 90% as compared to positive control group. The UI was almost same in group V and VI. TLM also showed marked inhibition of gastric lesions and protected the gastric mucosa in dose dependent fashion from 72.7 %, 81.80 % and 90.8 %. Percentage inhibition of test compound was comparable with omeprazole which also showed 90 % inhibition of gastric ulcer. Research work conducted by Adhikary et al. (2011) reported reduction of UI by 75 % in standard drug treated group and 81.7 % in *Epigallocatechin gallate* treated group[14]. Result of *Epigallocatechin gallate* almost resembles to that of the plant under study.

The histopathological evaluation in positive control group revealed topical erosions and disruptions of gastric mucosa. Hemorrhagic ulcers, edema, necrosis, vasocongestion, fibrosis and marked leucocyte infiltration were also observed in gastric tissue in diseased group as compared to healthy group. Microscopic findings in present study were consistent with other co-researchers[13, 20]. Mice that received TLM had comparatively better antiulcer changes. In comparison with diseased group significant reduction in ulcers and hemorrhages by 67%, 83 % and 87 % with TLM treated in dose dependent manner respectively. Erosion was decreased by 50 % in group III, 67 % in group IV and 67 % in group V than group II. There was almost no edema with maximum dose of TLM and nonsignificant decrease by 67 % with minimum dose of TLM and 83 % with maximum dose of TLM than positive control group. Dose dependent decrease in inflammatory exudate was observed in plant TLM treated groups by 33 % in group III, 50% in group IV and 67 % in group V as compared to positive control group. A reduction in vasocongestion by 83%, 67 %, 67 % in TLM treated groups respectively.

Simultaneously, group VI (omeprazole 3 mg/kg) depicted remarkable reduction in ulceration, hemorrhages, vasocongestion, fibrosis and edema by 83% in each observation as compared to positive control group. A nonsignificant decrease in inflammation by 33% and erosion by 67% was

observed in standard group as compared to group II. Omeprazole treated animals showed comparable antiulcer effect than TLM treated groups. The efficacy of plant extract in median and maximum doses was almost similar to omeprazole. The similar observation are in agreement with other studies [13,14].

The present study confirmed the findings pertaining to healing properties of TLM and attributed to the presence of gallic acid, flavonoids, tannins, saponins and polyphenol[20]. Zhang et al. (2022) also agreed that flavonoids boost cytoprotective, antioxidative, anti-inflammatory, and antibacterial defenses against peptic ulcer. Usually, one type of flavonoid can exhibit anti-ulcer roles through multiple mechanisms[21]. Further studies are required to evaluate the efficacy of flavonoids and other phytochemical constituents within the plant extract in preventing and treating peptic ulcer diseases.

CONCLUSION

TLM showed effectiveness against indomethacin induced gastric ulcer in mice. The plant extract successfully improved the gross and histopathological manifestations of stomach. TLM increased the gastric pH and decreased the volume of gastric juice. Current findings further suggest that TLM possess the anti-ulcer, antisecretory and anti-inflammatory properties.

Besides, the results obtained in this experimental study it is recommended that further extracts and isolates from *T. leptophylla* could be utilized for the development of new phytotherapeutic agents to medicate gastric ulcers. Furthermore, its efficacy should be assessed as a therapeutic agent on other models of gastric ulcers.

CONFLICT OF INTEREST

This research work reports no conflict of interest to be declared by any author.

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The Authors:

Dr. Saba Batool,
Assistant Professor,
Department of Pharmacology,
Nishtar Medical University, Multan.

Dr. Sheikh Maria Qammar,
Assistant Professor,
Department of Pharmacology,
Rashid Latif Medical and Dental College, Lahore.

Dr. Tooba Malik,
Assistant Professor,
Department of Pharmacology,
Services Institute of Medical Sciences, Lahore.

Prof. Dr. Naseem Saud Ahmad,
HOD of Pharmacology,
Department of Pharmacology,
Superior University, Lahore

Dr. Bushra Shaheen,
Assistant Professor,
Department of Pharmacology,
Bakhtawar Amin Medical and Dental College,
Multan.

Dr. Javaria Fatima,
Demonstrator,
Department of Pharmacology,
Fatima Jinnah Medical University,Lahore.

Corresponding Author:

Dr. Saba Batool,
Assistant Professor,
Pharmacology Department,
Nishtar Medical University, Multan.
Email: sababatool16@gmail.com